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Rec'd PCT/PTO 8 JUN 2006

Translation

## PATENT COOPERATION TREATY

## PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY  
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>K-1JST-OS</b>	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. <b>PCT/JP2004/004090</b>	International filing date (day/month/year) <b>24.03.2004</b>	Priority date (day/month/year) <b>25.03.2003</b>	
International Patent Classification (IPC) or national classification and IPC			
<p>Applicant <b>JAPAN SCIENCE AND TECHNOLOGY AGENCY</b></p>			

<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of <u>3</u> sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input checked="" type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s))</p> <p><b>1 disk</b>, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>																								
<p>4. This report contains indications relating to the following items:</p> <table> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input checked="" type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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<input type="checkbox"/>	Box No. VIII	Certain observations on the international application																						

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/JP2004/004090

## Box No. I

## Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

This report is based on translations from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of:

international search (Rule 12.3 and 23.1(b))  
 publication of the international application (Rule 12.4)  
 international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):

the international application as originally filed/furnished  
 the description:

pages 1-35 as originally filed/furnished

pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

the claims:

nos. 1-14, 16-19, 22-24, 26 as originally filed/furnished

nos.\* \_\_\_\_\_ as amended (together with any statement) under Article 19

nos.\* 15, 20, 21, 25 received by this Authority on 20.01.2005

nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

the drawings:

sheets fig. 1-6 as originally filed/furnished

sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3.  The amendments have resulted in the cancellation of:

the description, pages \_\_\_\_\_  
 the claims, nos. \_\_\_\_\_  
 the drawings, sheets/figs \_\_\_\_\_  
 the sequence listing (specify): \_\_\_\_\_  
 any table(s) related to sequence listing (specify): \_\_\_\_\_

4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

the description, pages \_\_\_\_\_  
 the claims, nos. \_\_\_\_\_  
 the drawings, sheets/figs \_\_\_\_\_  
 the sequence listing (specify): \_\_\_\_\_  
 any table(s) related to sequence listing (specify): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.  
PCT/JP2004/004090Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

## 1. Statement

Novelty (N)	Claims 2, 3, 8, 13-26	YES
	Claims 1, 4-7, 9-12	NO
Inventive step (IS)	Claims 2, 3, 13-26	YES
	Claims 1, 4-12	NO
Industrial applicability (IA)	Claims 1-26	YES
	Claims _____	NO

## 2. Citations and explanations (Rule 70.7)

Claims 1, 4 to 7 and 9 to 12

The inventions set forth in claims 1, 4 to 7 and 9 to 12 lack novelty in the light of document 1.

Document 1 discloses the feature of creating micromass cultures from limb mesenchymes that have been derived from a transgenic embryo, inducing the formation of cartilage by means of BMP-2 and BMP-4 (example 3) and then using the resulting cartilage in transplants (claims 23 to 26); therein, said cultures can be considered to include bone marrow stromal cells.

In addition, document 1 also compares the levels of differentiation that are induced by differentiation-inducing agents other than BMP-2 or BMP-4, or by candidate differentiation-inducing agents (examples 1, 2 and 4 to 6).

Meanwhile, the applicant asserts that although the micromass cultures of the limb mesenchymes that have been derived from an embryo include undifferentiated stem cells, said stem cells exhibit various characteristics and/or stages of differentiation; asserts that document 1 does not disclose or suggest the feature wherein the differentiation-inducing agents such as BMP-2 and BMP-4 are only brought into contact with the bone marrow

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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Box No. V

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

stromal cells; and asserts that in the preferred embodiments of the invention set forth in present application, cell lines that exhibit a clear differentiation direction are employed as the cultivation system and the characteristics of the stromal cells are made clear, whereas document 1 does not suggest such a configuration.

However, the inventions that are set forth in claims 1, 4 to 7 and 9 to 12 are not limited to configurations in which the multipotent stem cells are included within a prescribed uniform cell population, and the only condition is that multipotent stem cells which are capable of growth be included; therefore, it is impossible to say that cultures which include a plurality of types of cells do not fall within the scope of the present invention. As a result, the assertions of the applicant are not supported by the disclosures in the claims; therefore, said assertions are not applicable.

Consequently, the inventions that are disclosed in document 1 cannot be differentiated from the inventions that are set forth in claims 1, 4 to 7 and 9 to 12.

#### Claim 8

The invention set forth in claim 8 does not involve an inventive step in the light of documents 1 to 2.

The invention that is disclosed in document 1 differs from the invention that is set forth in claim 8 of the present application in that document 1 does not disclose the feature wherein the multipotent cells are derived from a transgenic mouse that supports the temperature sensitive SV-40T antigen gene; however, transgenic mice that support the SV-40T antigen gene were

Box No. V

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

well known as a supply source for multipotent stem cells at the time the present application was filed, as disclosed in document 2.

Therefore, it would be easy for a person skilled in the art to substitute the transgenic mice that are disclosed in document 2 for the mice which serve as the stem cell acquisition source in the invention that is disclosed in document 1.

#### Claims 2, 3 and 13 to 26

The inventions set forth in claims 2, 3 and 13 to 26 involve an inventive step in relation to documents 1 to 2.

Documents 1 and 2 do not disclose the feature of treating the bone marrow stromal cells with a substance that is capable of promoting and/or inhibiting the differentiation of cells in at least two directions during the step for growing the bone marrow stromal cells. In addition, it cannot be said to be easy to conceive of the inventions that are set forth in claims 2, 3 and 13 to 26 in the light of the inventions that are disclosed in documents 1 and 2 and/or well-known and commonly used technical features, even for a person skilled in the art.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.  
PCT/JP2004/004090

## Box No. VI Certain documents cited

## 1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 03/066856 A1	14.08.2003	06.02.2003	06.02.2002

[E, X]

## 2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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## Supplemental Box Relating to Sequence Listing

## Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:
  - a. type of material
    - a sequence listing
    - table(s) related to the sequence listing
  - b. format of material
    - in written format
    - in computer readable form
  - c. time of filing/furnishing
    - contained in the international application as filed
    - filed together with the international application in computer readable form
    - furnished subsequently to this Authority for the purposes of search and/or examination
    - received by this Authority as an amendment\* on \_\_\_\_\_
2.  In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

\* If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."